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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/319,736	08/02/1999	ELISABETH WOLPERT	000500-182	3510

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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1643

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/319,736

Applicant(s)

WOLPERT ET AL.

Examiner

Karen A. Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 143-162 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 143-162 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/11/99+9/18/00</u> | 6) <input type="checkbox"/> Other: ____ |

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DETAILED ACTION

The request filed on October 23, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/319,736 is acceptable and a CPA has been established. An action on the CPA follows.

Acknowledgment is made of applicants election with traverse of the species of [c] a gene encoding a TAP inhibitor. The traversal is on the grounds that the election requirement is improper as the examiner did not explain the patentable differences between the species. This has been considered but not found persuasive. The M.P.E.P. make no provision for such explanation in the context of a species election versus a Restriction Requirement. Further, applicants arguments are not tenable as additional species will be examined in the event that the elected species are free of the art. Further, after reconsideration of the species election in light of the prior art, the species election requirement, mailed April 18, 2005 is withdrawn.

Claims 143-162 are pending and under consideration.

Claim 155 is objected to because of the following informalities: the typographical error of "claims 148" rather than "claim 148".. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 155-157, 160 and 161 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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Claim 157 is drawn to a composition comprising cells identified according to the method of claim 148. Claim 160 is drawn to cells identified according to the method of claim 148, antigens or epitopes expressed by said cells. Claim 161 is drawn to a composition comprising immunological effector cells identified according to the method of claim 155. It is noted that claims 157 and 160 are dependent upon the cell identified by the method of claim 148; the methods of claims 155 and 156 depend on the cells identified by the method of claim 148, and that claim 161 is a method reliant on the identity of cell identified by the method of claim 155, which in turn is reliant on claim 155 which is drawn to a process comprising stimulating isolated immunological effector cells in vitro with cell identified according to the method of claim[s] 148. The products of claims 157, 160 and 161 lack adequate written description, because the specification cannot adequately describe cells which have yet to be isolated. It logically follows that if a product itself is not adequately described, the method of using said product cannot be adequately described.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 143-147, 159 and 162 are rejected under 35 U.S.C. 102(e) as being anticipated by Nair et al (U.S. 5,831,068).

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Claim 143 is drawn to a method of impairing cellular processing for MHC presentation comprising treating cells with a substance, wherein the substance is characterized in that tumor cells treated with the substance are subject to specific lysis by CTL encoded by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule, B7-1, thereby inducing immunological effector cells specific for endogenous epitopes associated with impaired cellular processing. Claim 144 embodies the method of claim 143 wherein the substance is selected for the group consisting of substances which inhibit the function of TAP, and substances which inhibit the expression of TAP. Claim 145 embodies the method of claim 143, wherein the substance is selected from the group consisting of ICP-47 of HSV type 1, IE12 of HSV, type 2, a gene encoding for a TAP inhibitor, a nucleotide sequence that is complementary to the polynucleotide encoding TAP, anti-sense oligonucleotides, and RNA destroying ribozymes. Claim 146 embodies the method of claim 143 wherein the substance inhibit the function and expression of the proteasome. Claim 147 embodies the method of claim 123, wherein the substance is selected from the group consisting of a peptide aldehyde, Z-Leu, Leu, Lactacystin, DNA encoding a proteasome inhibitor, a nucleotide sequence that is complementary to at least a part of the mRNA or DNA sequence encoding the proteasome, anti-sense and RNA-destroying ribozyme.

Claim 159 is drawn to a composition comprising a substance that impair peptide processing for MHC presentation and thereby induces immunological effector cell specific for endogenous epitopes associated with impaired cellular processing for MHC presentation, the substance being characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected with the stimulatory molecule B7.1; and a pharmaceutically acceptable adjuvant selected from cytokines, genes for cytokines, costimulatory molecules, gold beads and/or liposomes. Claim 162 is drawn to a kit comprising a substance that impairs cellular peptide processing for MHC presentation, and thereby inducing immunological effector cells specific for endogenous epitopes associated with impaired cellular peptide processing for MHC presentation, the substance being characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transfected

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with the stimulatory molecule B7-1; and cytokines, genes for cytokines, costimulatory molecules, gold beads and/or liposomes.

Nair et al teach a method of inhibiting MHC I pathway associated components in a cell which include cells deficient in a TAP protein activity or proteasome activity, prior to contacting said cell with an antigen (column 1, lines 60-64). Nair et al teach the introduction into a cell of a anti-sense oligonucleotide which is complementary to said MHC-pathway dependent protein, introduction into said cell of an RNA decoy which binds to an MHC I pathway associated protein, introduction of a ribozyme which specifically cleaves mRNA encoding an MHC I pathway associated protein into a cell, introduction of proteasome inhibitors such as lactacystin (column 2, lines 1-35). Nair et al teach cells comprising anti-sense inhibitors of TAP-2 (column 16, examples II and III), cells dendritic cells contacted with proteasome inhibitors (column 20, Example IX) which fulfills the specific embodiment of claims 153 and 154.

Nair et al disclose a composition comprising an anti-sense genetic construct including all or a portion of a gene encoding TAP-1 (column 8, lines 16-18) in combination with a lipid (column 8, lines 38-41) thus fulfilling the specific embodiment of a substance that impairs cellular processing for MHC presentation as defined by claims 159 and 162, and a liposome.

Claims 155-157, 160 and 161 are rejected under 35 U.S.C. 102(b) as being anticipated by Hammond et al (Nature, 1993, Vol. 364, pp. 158-161).

The specific embodiments of the claims are set forth above. Hammond et al disclose T2-A3 cells expressing wild-type env or gp120 protein and the clone A3.1, which lysed said cells (page 158, second column, lines 19-26). It is noted that the recitation of limitations as regards the "substance" in claim 148 defines said substance, but does not confine the treated cells to tumor cells which have been transfected with B7-1. Hammond et al anticipate the instant claims because the M.P.E.P. (2113) states:

**PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE
MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY
THE STEPS.**

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Claims 155-157, 160 and 161 are rejected under 35 U.S.C. 102(a) as being anticipated by Wolpert et al (PNAS, Oct 1997, Vol. 94, pp. 11496-11501). Wolpert et al disclose RMA-S as a TAP2 deficient cell line and RMA-S.B-1 which is the RMA-S cell line transfected with B7-1 (page 11496, second column, under the headings "Cell lines" and "Transfection of RMA-S with B7-1"), both cell lines meeting the specific embodiments of claims 157 and 160, because the cell lines bind to immunological effector cells that selectively recognize TAP2 deficient cells. Wolpert et al disclose a method of stimulating CTL in vitro with cells that show impaired cellular peptide processing for MHC presentation (page 11497, second column, under the heading "Efficient CTL Recognition of TAP-Deficient Cells Requires the Presence of MHC Class I Molecules and the Absence of TAP in the Target Cell" and page 11498, first column, under the heading "Generation of Primary CTLs Specific for TAP-Deficient Cells"), thus meeting the limitations of claim 155, because the cells identified by the method of claim 148 are set forth by the claims as a product by process and the M.P.E.P. (2113) teaches that product-by process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 148-158, 160 and 161 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nair et al (U.S. 5,831,068) in view of Sanberg et al (Eur Journal of Immunology, 1996, Vol. 26, pp. 288-293) and Skipper et al (Journal of Experimental Medicine, 1996, Vol. 183, pp. 527-534).

The specific embodiments of claims 155-157, 160 and 161 are recited above.

Claim 148 is drawn to a process comprising treating cells in vitro with an effective dose of a substance that impairs cellular peptide processing for MHC presentation, wherein the substance is characterized in that tumor cells treated with the substance are subject to specific lysis by CTL elicited by endogenous MHC I dependent antigens of the TAP-deficient variant of said tumor cell which has been transected with the stimulatory molecule B7-1, and identifying cells which activate CD8 T lymphocytes that selectively recognize cells having endogenous epitopes associated with impaired cellular peptide processing for MHC presentation. Claim 149 embodies the process of claim 148 wherein the substance inhibits the function and/or expression of TAP. Claim 150 embodies claim 149, wherein substance is selected from the group consisting of ICP-47 of HSV type 1, IE12 of HSV, type 2, a gene encoding for a TAP inhibitor, a nucleotide sequence that is complementary to the polynucleotide encoding TAP, anti-sense oligonucleotides, and RNA destroying ribozymes. Claim 151 embodies the method of claim 146, wherein the substance inhibits the function and expression of the proteasome. Claim 152 embodies the method of claim 151, wherein the substance is selected from the group consisting of a peptide aldehyde, Z-Leu, Leu, Lactacystin, DNA encoding a proteasome inhibitor, a nucleotide sequence that is complementary to at least a part of the mRNA or DNA sequence encoding the proteasome, anti-sense and RNA-destroying ribozyme. Claim 153 embodies the process of claim 148, wherein the cells are autologous cells/hematopoietic cells. Claim 154 embodies the method of claim 153 wherein the autologous and/or hematopoietic cells are dendritic cells, or cells from cancer tissues.

Claim 155 is drawn to a process comprising stimulating isolated immunological effector cells in vitro with cells identified according to the method of claims 148 and identifying

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immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation. Claim 156 embodies the process of claim 155 wherein the immunological effector cells are CD8+ T lymphocytes.

Claim 157 is drawn to a composition comprising cells identified according to the method of claim 148.

Claim 158 is drawn to a process comprising administering to a mammal immunological effector cells that selectively recognize cells showing impaired cellular peptide processing for MHC presentation.

Claim 160 is drawn to cells identified according to the method of claim 148 or antigens or epitopes expressed by such cells and a pharmaceutically acceptable additive.

Claim 161 is drawn to a composition comprising immunological effector cells identified according to the method of claim 155.

Nair et al teach methods of identifying cells which activate CD8+ lymphocytes in vitro (column 17, example IV and V) and methods comprising administering to a mammal CTL which recognize cells treated to eliminate a MHC I pathway associated protein. Nair et al do not teach endogenous epitopes associated with impaired cellular processing because Nair et al exposes said MHC I pathway deficient cells to exogenous peptides, therefore the immunological effector cells taught by Nair et al are not specific to the peptides associated with impaired cellular processing.

Sandberg et al teach that TAP1 deficient mice have a diverse CD8+ T cell repertoire that provides peptide-specific CTL (page 289-290, section 3.1 and page 290-291, section 3.3). Sandberg et al teach that these peptides are limited to those generated in the endoplasmic reticulum, such as those derived from signal sequences and those entering the ER independently of TAP (page 291, second column, lines 36-39 and page 292, first column, lines 1-2).

Skipper et al teach a peptide which is recognized by a CTL clone which recognizes the tyrosinase gene product on melanoma cells. Skipper et al teach that said peptide exhibits a posttranslational conversion of asparagine to aspartic acid. Skipper et al conclude that said post-translationally modified peptide is processed through the ER (abstract, last sentence). Skipper et al suggest that such post-translational changes can lead to the generation of new antigens which are relevant to tumor rejection (page 532, second column, lines 21-27).

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It would have been prima facie obvious at the time the invention was made to carry out the methods of Nair et al without the subsequent step of pulsing the MHC I pathway deficient cells with exogenous peptides, and to use the resulting cells in a method of isolated specific CTL clones. One of skill in the art would have been motivated to do so by the teaching of Sanberg et al on the polyclonal nature of the T cell repertoire possible in TAP deficient transgenic mice, and the antigens derived from proteins via endoplasmic reticulum for presentation in a MHC I, TAP-independent mechanism, and by the teachings of Skipper et al on the possibility of new antigens afforded by proteins targeted to the ER by TAP independent mechanism, and the suggestion of Skipper et al that peptides derived from the ER, rather than the TAP pathway could represent a pool of new antigens important to tumor rejection.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

8/8/2005


KAREN A. CANELLA PH.D.
PRIMARY EXAMINER